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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,001	04/21/2000	Joan C. Egrie	A-460A	1458

21069 7590 07/18/2003

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	21

DATE MAILED: 07/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/559,001	EGRIE ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The finality of the rejection of the last Office Action is *withdrawn* in view of the new grounds of rejection set forth below.

Status of Application, Amendments and/or Claims

The amendment filed 05 May 2003 (Paper No. 20) has been entered in full. Claims 45-60 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejections of claims 45-60 under 35 USC 112, first paragraph, written description as set forth at pages 3-5 of the previous Office Action (08 November 2003, Paper No. 18) is *withdrawn* in view of Applicant's arguments (05 May 2003, Paper No. 20).

Claim Rejections - 35 USC § 112, First paragraph, Enablement

Claims 45 and 51-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or

more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site. The specification teaches that alterations of Epo carbohydrate chains can affect biological activity. Some changes increase *in vivo* activity, other changes increase serum half-life but decrease affinity for the Epo receptor. The instant invention provides for a method of raising and maintaining hematocrit in a mammal comprising administering a therapeutically effective amount of an Epo hyperglycosylated analog.

The specification teaches that Epo hyperglycosylated analogs have shown *in vitro* activity which was comparable to *or even less than* that determined for rHuEpo, suggesting that binding to the Epo receptor is not enhanced, and may in some cases be diminished, by addition of carbohydrate chains. However, hyperglycosylation can typically increase serum half-life and potentially lead to increased *in vivo* biological activity (page 11, lines 26-36). The specification teaches the introduction of N-linked glycosylation sites at specific residues in human erythropoietin (pages 34, 36 and 40) and employs various assays to discern activity (pages 45,-57).

The instant claims recite "at about position" which encompasses the introduction of N-linked glycosylation sites not taught by the specification. The specification teaches that Epo hyperglycosylated analogs have shown *in vitro* activity which was less than that determined for rHuEpo, suggesting that binding to the Epo receptor is not enhanced. Thus, changes made in certain residues of erythropoietin can affect the biological activity. The specification is not enabled for any amino acid change which

would provide for an N-linked glycosylation site. As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases (see Wells, 1990, Biochemistry 29:8509-8517). Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, Sec nd paragraph

Claims 45 and 51-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site.

The term "at about position" is a relative term which renders the claim indefinite. The term "at about position" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102(b)

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 45 and 51-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliott *et al.,* WO 95/05465 (reference submitted by Applicant, IDS #BC, Paper No. 5). Elliott *et al.* teach carbohydrate attachments of asparagine residues (N-linked) at positions 30, 51, 57, 69, 88, 89, 136 and 138 in the human erythropoietin amino acid sequence (page 15, lines 16-33 and page 56 Table 6). Elliott *et al.* therefore teach an

analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced **at about position** 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site.

Elliott *et al.* teach DNA sequences encoding such erythropoietin analogs, recombinant plasmids and host cells for analog expression (page 5, lines 22-25). Elliott *et al.* also teach pharmaceutical compositions comprising a therapeutically effective amount of an erythropoietin analog together with a suitable diluent, adjuvant and/or carrier (page 20, lines 23-36).

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53, 54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.* (WO 95/05465), IDS #BC in view of Yoshitomi *et al.*, US Patent No. 5,559,093. The teachings of Elliott *et al.* are described above. Elliott *et al.* do not teach citrate as a diluent, human serum albumin as a carrier or benzyl alcohol as a preservative in compositions comprising an analog of human erythropoietin.

Yoshimito *et al.* teach administering a platelet-increasing agent (hst-1). Yoshimito *et al.* teach that hst-1 can be administered in combination with other platelet increasing agents such as erythropoietin (column 8, lines 8-22). Yoshimito *et al.* teach pharmaceutical compositions, pharmaceutical acceptable additives, diluents or excipients (column 8, lines 28-31). Yoshimito *et al.* teach the use of sodium citrate, human serum albumin and benzyl alcohol (column 8, lines 31-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings Elliott *et al.* and Yoshimito *et al.* to make the instant invention of a composition comprising an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an

N-linked carbohydrate chain is attached at said one additional site and citrate, human serum albumin and benzyl alcohol. The motivation and expected success comes from the benefits of stabilizing/preserving, antibacterial action and proper buffering (pH) of hyperglycosylated erythropoietin analogs which is provided by using sodium citrate, human serum albumin and benzyl alcohol.

Claim 55 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.* (WO 95/05465) in view of Igari *et al.*, US Patent No. 5,416,071.
The teachings of Elliott *et al.* are described above. Elliott *et al.* do not teach the use of tween in compositions comprising an analog of human erythropoietin. Igari *et al.* teach a composition for sustained release of erythropoietin comprising erythropoietin and a pharmaceutical carrier (column 4, lines 12-21). Igari *et al.* teach the use of tween with erythropoietin (column 7, lines 21-34 and lines 42-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Elliott *et al.* and Igari *et al.* to make the instant invention of a composition comprising an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site and tween. The

motivation and expected success comes from the use of Tween® in pharmaceutical compositions which provides the benefit of solubilization.

Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.* (WO 95/05465) in view of Young *et al.,* US Patent No. 6,548,653 B1. The teachings of Elliott *et al.* are described above. Elliott *et al.* do not teach the use of ascorbic acid or sodium metabisulfite in compositions comprising an analog of human erythropoietin. Young *et al.* teach a pharmaceutical composition comprising erythropoietin analog-human serum albumin fusion protein (EPOa-hSA) (column 30, lines 34-40). Young *et al.* teach intravenous administration of EPO-hSA with ascorbic acid (column 30, line 65-column 31, line 6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Elliott *et al.* and Young *et al.* to make the instant invention of a composition comprising an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site and ascorbic acid. The motivation and expected success comes from the use of ascorbic acid in pharmaceutical compositions which provides antibacterial and/or antifungal benefits.

Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.* (WO 95/05465) in view of Kawaguchi *et al.*, US Patent No. 4,806,524. The teachings of Elliott *et al.* are described above. Elliott *et al.* do not teach lyophilized forms of erythropoietin or the use of amino acids such as lysine, glycine. Kawaguchi *et al.* teach liquid and freeze dried (lyophilized) forms of erythropoietin (column 1, lines 43-50; column 2, lines 16-27; column 2, lines 45-67). Kawaguchi *et al.* teach stable preparations of erythropoietin for pharmaceutical use. Kawaguchi *et al.* disclose erythropoietin stabilizers such as lysine and glycine (column 1, line 64-column 2, lines 11 and Table).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Elliott *et al.* and Kawaguchi *et al.* to make the instant invention of a composition comprising an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site, wherein the composition further comprises an amino acid and is in liquid or lyophilized form. The motivation and expected success comes from the use of lyophilization and amino acids in pharmaceutical compositions which provide the benefit of stable storage.

Claim Objections

Claims 47 and 48 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The basis for this rejection is set forth at page 5 of the previous Office Action (08 November 2003, Paper No. 18).

Applicant states that claim 47 has been amended to place in claim in proper dependent form. Applicant's arguments have been fully considered but not deemed persuasive for the following reasons. The instant claims do not claim every limitation of the parent claim. Claims 47 and 48 have substitutions at sites which were not recited in the independent claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

RMD
July 1, 2003

Gary L. Kunz

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